REMARKS/ARGUMENTS

Claims 2-4 and 7-10 are cancelled.

Claim 11 is new.

Support for each new and amended claim is found at the originally filed claims and throughout the specification.

Upon entry of the amendment, Claims 1, 5-6, and 11 will be active.

No new matter is believed to have been added.

The sequence compliance issue has been addressed by assigning a SEQ ID NO to the sequences in need thereof at page 25.

The indefiniteness rejection of Claims 1-10 is respectfully traversed. The rejection of Claims 2-4 and 7-10 is obviated by cancellation of these claims. The rejection of Claim 1 is obviated as follows: the term "dimer" has been changed to "homodimer" to clarify the composition of the dimer; the phrase "capable of producing a tumor antigen peptide having CTL inducing activity" has been clarified to read "has CTL inducing activity;" and the phrase "bound each other" has been clarified to "bound to each other." Withdrawal of the indefiniteness rejection is respectfully requested.

The 35 U.S.C. 101 rejection of Claim 9 is obviated by cancellation of Claim 9.

The enablement rejection of Claims 7-10 is obviated by cancellation of Claims 7-10.

The obviousness rejection of Claims 1-8 as being unpatentable over EP1103564 or EP 1371664 or Gaiger in view of Marastoni and Di modugno is respectfully traversed, because the references do not describe or suggest all of the features of the present claims. The rejection of Claims 2-4 and 7-8 is obviated by cancellation of these claims.

The Office has characterized Marastoni as "disclosing that dimerization of monomers improves the binding to HLA-A2 molecules and this can lead to inducing efficient CTL

responses." (See page 10 of the Official Action). Applicants respectfully submit this characterization is incorrect.

Applicants note that present Claim 1, for example, is drawn to a peptide homodimer. The Abstract of Marastoni describes dimers, not homodimers. More importantly, only one of the dimers in Table I of Marastoni (see Table 1, page 594), entry 1, is a homodimer, with the rest of the entries being control mono peptide (CLG) or containing spacers or being heterodimers (entries 2-9 of Table 1, page 594, of Marastoni). When entry 1, the sole homodimer, was tested, the homodimer was slightly less active than the control mono peptide (see Figure 2, graph on the left hand side, line with circular data points and line with square data points). Further, Marastoni does not disclose any data showing CTL-inducing activity. Accordingly, one of ordinary skill in the art would conclude, based on the disclosure of Marastoni, that the homodimerization of peptides would not be expected to improve binding affinity to binding to HLA-A2 molecules, and that no conclusion about CTL-inducing activity of homodimers could be drawn, because Marastoni does not disclose any CTL-inducing data.

The Office has characterized Di Modugno as follows: "Di Modungo discloses the use of cysteines to form disulfide bonds in homodimers and that this increased the generation of different confirmations which can lead to increased anti-tumor immune response." (See the Official Action at page 4). Applicants respectfully submit that the Office has mischaracterized, in part, Di Modugno.

The purpose of Di Modugno, as described at page 35, left column, second paragraph through final paragraph, is to examine whether ErbB-2 rich in cysteine can form a dimer containing cysteines *in vivo*, and be presented to an HLA. As described in the Official Action at page 4, Applicants agree to the extent that "the use of cisteines to form disulfide

bonds in homodimers....increases the generation of different conformations..." Dimerization of a peptide results in drastic structural changes. Because of this, one of ordinary skill in the art would not know if CTL's induced by a dimer would recognize natural-type peptides existing in a living body. Further, the binding affinity of homodimer for HLA-A2 is even lower than for the monomer (See Fig.2, the 48 dim and 789 dim, of Di Modugno). Di Modugno does not examine CTL-inducing activity. Accordingly, one of ordinary skill in the art would find that homodimers are less active than monomers for HLA-A2 biding, that the ability of a homodimer to induce CTL-inducing activity is unknown, and that it is unknown if CTLs induced by a dimer would recognize natural type peptides existing in the living body.

Accordingly, the references do not describe or suggest all of the features, of, for example, present Claim 1. Withdrawal of the obviousness rejection, on this basis alone, is respectfully requested.

Applicants have submitted, along with this paper, an inventor's declaration.

Applicants note that the present inventors have found, for the first time, that a homodimer of a tumor antigen peptide has CTL-inducing activity *in vivo*. Specifically, when the present inventors administered a peptide homodimer derived from the tumor antigen WT1 (SEQ ID NO: 1) to a subject and confirmed that the homodimer is able to induce peptide specific CTL's *in vivo* for the first time. (See Results at page 2 of the declaration and Figure 1 of page 3 of the declaration).

A peptide of generally about 8-10 amino acids binds to an MHC class I antigen (HLA antigen) to form a complex recognized by CTL's. (See Di Modugno, page 431, Summary, lines 1-4).

The mechanism is easily understood by referring to the Scientific American article submitted along with this paper. In the Figure at page 36 of the Scientific American article,

the mechanism is illustrated in detail. A complex of the cancer antigen peptide and an MHC class I antigen is presented on the cell surface, which is recognized by CTLs through the antigen receptor portion.

It was, however, utterly unclear whether or not a homodimer, as described in, for example, present Claim 1, having a structure which is different from a standard 8-10 amino acid peptide monomer, would, even if bound to an MHC class 1 antigen, be recognized by CTLs.

The present inventors have conducted experiments using the peptide homodimer of SEQ ID NO: 44 and confirmed that the homodimer has specific cross reactivity and is useful for a pharmaceutical composition (see Inventor's Declaration).

The peptide homodimer used in Test Example 1 is a dimer composed of a variant peptide (SEQ ID NO: 44) having an amino acid sequence derived from a WT1 (position 234-243) peptide (SEQ ID NO: 11) by altering the methionine residue at position 2 to be tyrosine. Both peptides are shown in Table 4 of the present specification.

It was therefore surprising, based on what was known at the time of filing of the present application, that CTL's induced by a dimer recognized a monomer, and that CTL's induced by a dimer had a cross-reactivity and recognized the natural-type peptide monomer.

Cancer cells in a living body present a peptide monomer on MHC class I antigen as illustrated in Figure 1 of the inventor's declaration. Accordingly, a peptide dimer would not be expected to be useful as a therapeutic agent if CTLs induced by administration of the peptide dimer do not recognize a peptide monomer.

Furthermore, when the peptide dimer is composed of a variant peptide as mentioned above, such a dimer cannot be used as a therapeutic agent unless the induced CTLs do

recognize a natural type peptide monomer (e.g., not altered native peptide), since cancer cells in a living body present a peptide monomer of the natural type.

These problems have been addressed by the presently claimed inventive embodiments, as shown by the data in the attached declaration.

The present inventors, in Experiment 2 of the declaration, have also shown that, after three minutes in blood, more than 65% of a homodimer remained unchanged while only less than 5% of monomers remained unchanged. Thus, the homodimer is far more stable than monomers in the blood.

The above results, based on what was known at the time of the application's filing, are unexpected and superior. Applicants request withdrawal of the obviousness rejection.

Applicants submit the present application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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